silence Nrf2 expression. SFN significantly up-regulated Nrf2 and also prevented Ang II-induced CTGF and PAI-1expression, which were completely abolished by Nrf2 silence. Furthermore, Nrf2-TG mice were highly resistant to Ang II-induced cardiac pathogenic changes and cardiac dysfunction. To dissect the mechanism for SFN activation of Nrf2, H9c2 cells were given SFN (10 μM) simultaneously with and without Akt inhibitor (LY294002, 10 μM). SFN's activation of Nrf2 was partially inhibited by Akt inhibition that also induced GSK-3β activation and Fyn nuclear accumulation.
Conclusions: Ang II-induced cardiomyopathy can be prevented by SFN via Akt/GSK-3β/Fyn-mediated activation of Nrf2 antioxidant pathway.

GW25-e4230

Post-ischemic myocardial insulin resistance induced by TNF-α overproduction precipitates the development of heart failure after myocardial infarction

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Objectives: Clinical evidence has demonstrated a decreased myocardial insulin response in heart failure (HF) patients. The objective of this study is to investigate the role of myocardial insulin resistance in the development of ischemic HF and its underlying mechanisms.
Methods: Adult male Sprague Dawley rats were subjected to a permanent occlusion of the left anterior descending coronary artery. Cardiac function and remodeling were evaluated by echocardiographic. Insulin stimulated myocardial fluorodeoxyglucose (FDG) uptake were measured by micro-PET/CT.
Results: Rats subjected to myocardial infarction (MI) resulted in a progressive left ventricular (LV) remodeling and dysfunction. Echocardiographic assessment showed preserved LV end-systolic dimension (LVESD 0.453±0.027 cm) and ejection fraction (EF 57.03±2.35%) at 1 week after MI, and evident LV dilation (LVESD 0.621±0.026 cm) and dysfunction (EF 40.12±3.09%) at 4 weeks. Myocardial insulin sensitivity decreased significantly at 1 week after MI as evidenced by reduced insulin-stimulated myocardial fluorodeoxyglucose uptake (Standardized Uptake Value: 2.71±0.42 vs. 5.13±0.51 of sham+insulin, n=6, P<0.01) and GLUT-4 translocation and altered insulin signaling. Meanwhile, MI increased myocardial TNF-α production. Treatment with Etanercept (a TNF-α inhibitor) during the first week following MI improved myocardial insulin sensitivity, while adenovirus-mediated cardiac overexpression of TNF-α resulted in myocardial insulin resistance in non-MI hearts. In addition, TNF-α overexpressed rat hearts exhibited LV dysfunction (EF 41.32±4.21%) and LV dilation (LVESD 0.627±0.036 cm) as early as 1 wk after MI. More importantly, tamoxifen-induced cardiomyocyte-specific insulin receptor knockout mice developed aggravated post-ischemic LV remodeling and dysfunction compared with littermate controls (EF 31.54±2.41 vs. 45.32±2.65 %, LVESV 31.54±2.41 vs. 45.21±2.65 μl, both P<0.05). Insulin treatment during the first week following MI not only suppressed myocardial TNF-α production and increased myocardial insulin sensitivity, but also alleviated cardiac dysfunction and remodeling at 4 wk after MI.
Conclusions: Myocardial insulin resistance induced at least partly by TNF-α overproduction following MI contributes to the development of post-ischemic HF, which indicates an essential role of myocardial insulin signaling in protection against ischemic HF.

GW25-e4306

Angiotensin-(1-7) stimulates cholesterol efflux from angiotensin II-treated cholesterol-loaded THP-1 macrophages through suppression of p38 and JNK signaling

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Objectives: Angiotensin II (Ang II) and angiotensin-(1-7) (Ang-(1-7)) are key effector peptides of the renin-angiotensin system. The aim of this study is to investigate the effects of Ang-(1-7) on Ang II-stimulated cholesterol efflux and associated molecular mechanisms.
Methods: Differentiated THP-1 macrophages were treated with Ang II (1 μM) and/or Ang-(1-7) (10 and 100 nM) for 24 h and cholesterol efflux and gene expression were assessed. Pharmacology inhibition of peroxisome proliferator-activated receptor gamma (PPARγ) and mitogen-activated protein kinases (MAPKs) were done to identify the signaling pathways involved.
Results: Our results showed that Ang II significantly inhibited cholesterol efflux from cholesterol-loaded THP-1 macrophages. Ang-(1-7) led to a dose-dependent restoration of cholesterol efflux in Ang II-treated cells. The co-treatment with Ang-(1-7) and Ang II significantly increased the ABCA1 and ABCG1 expression relative to treatment with Ang II alone, which was coupled with increased expression of PPARγ and liver X receptor alpha (LXRα). Pharmacological inhibition of PPARγ significantly (P<0.05) abolished Ang-(1-7) -mediated induction of ABCA1 and ABCG1 mRNA expression. Ang-(1-7) treatment caused an inactivation of JNK and p38 MAPK signaling in Ang II-treated THP-1 macrophages. Moreover, inhibition of JNK or p38 MAPK signaling using specific pharmacological inhibitors mimicked the induction of PPARγ and LXRα expression by Ang-(1-7).
Conclusions: Taken together, our data demonstrate that Ang-(1-7) promotes cholesterol efflux in Ang II-treated THP-1 macrophages in part through inactivation of p38 and JNK signaling and induction of PPARγ and LXRα expression and may thus have therapeutic benefits in atherosclerosis.

GW25-e4414

Berberine improves coronary vasodilation and prevents endothelial apoptosis via activating Akt-eNOS in diabetic rats

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Objectives: The impaired endothelial cells are the major cause of vessel dysfunction in diabetes. Berberine, an isoquinoline alkaloid, has been demonstrated to lower blood glucose and regulate lipid metabolism disorders, while the mechanism of protection of berberine in diabetic cardiovascular disease remains elusive. In present study, we sought to study the effects of berberine on diabetes coronary artery vessel dysfunction and the underling mechanisms.
Methods: Diabetic rat were induced by injected streptozotocin and fed with a high-fat diet for 12 weeks. Rats were randomized to receiving saline or berberine treatments (200 mg/kg/d, gravage) in the last 4 weeks. HUVECs were cultured in HG/HF (25 mmol/L glucose DMEM and 500 μmol/L palmitate) to simulate the damage endothelial dysfunction of diabetes in vitro.
Results: Coronary arteries from berberine treated diabetic rats exhibited an obvious ACh-induced vasodilatation enhancement. Moreover, berberine treatment improves the insulin mediated vasodilatation of coronary artery compared with the diabetic rats (26.6% *vs.* 3.2%, n=12, *P*<0.01). More interestingly, the beneficial effects of berberine on vasodilatation were blunted by wortmannin, an inhibitor of PI3K/Akt. According to TUNEL staining, treatment of berberine significantly attenuated diabetic rats coronary artery endothelium apoptosis. *In vitro* study, berberine treatment reduced HG/HF-induced HUVECs apoptosis, increased Bcl-2/Bax ratio and decreased caspase-3 expression significantly, together with enhanced Akt, GSK3β and eNOS phosphorylation. While, pretreatment with either wortmannin or AMPK inhibitor Compound C, the anti-apoptotic effect of berberine were significantly blunted.
Conclusions: Berberine enhances vasodilatation and protects against endothelial apoptosis in diabetes rats coronary artery, which is mainly through the activation of the Akt-eNOS signaling.

GW25-e4425

High levels of circulating endothelial microparticles and increased tissue factor procoagulant activity of plasma microparticles in patients with acute coronary syndromes

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Objectives: Microparticles (MPs) are submicron vesicles released from activated or apoptotic cells and involved in message delivering. Elevated numbers of platelet microparticles (PMPs) and endothelial microparticles (EMPs) have been reported in patients with acute coronary syndrome (ACS). The purpose of this study was to assess levels and tissue factor procoagulant activity of circulating MPs in patients with ACS.
Methods: AnnexinVpositive MPs (AMPs), PMPs, CD31 positive EMPs, CD62E positive EMPs, and monocyte MPs (MMPs) were measured in 36 patients with ACS. We also enrolled 16 healthy individuals as normal controls. Calibrated automated thrombogram assay was used to evaluate the MP-mediated thrombin generation among ACS patients and normal controls. The lag time, time to peak, endogenous thrombin potential (ETP), peak thrombin generation between two groups were measured and compared. Furthermore, we investigated the association between variables such as numbers of MPs, lag time, endogenous thrombin potential, high-sensitivity C-reactive protein (hs-CRP), and peak value of cardiac troponin I (TnI).
Results: CD31 positive EMPs with the concentration of 1118 /μL were main circulating MPs in ACS patients. Through thrombin generation test, both the ETP (924.2±349.9 vs 652.3±146.7 nM×min, P=0.001) and the peak (87.5±39.6 vs 55.0±24.4 nM, P=0.002) increased in ACS patients compared with those of healthy. For ACS patients, the levels of AMPs were negatively correlated with the peak value of TnI (r_p= -0.416, P=0.028), while the levels of CD31 positive EMPs were negatively correlated with high-density lipoprotein cholesterol (HDL-C) (r_p= -0.493, P=0.009).
Conclusions: CD31 positive EMPs were the main circulating MPs presented in ACS patients. Compared to healthy, tissue factor procoagulant activity of plasma MPs increased in patients with ACS.

GW25-e5206

Role of perivascular adipose tissue-derived LET-7B in vascular inflammation VIA ADRB3

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Objectives: Vascular injury caused by hypertension is a chronic low-grade inflammation process, especially a growing number of studies have shown that inflammatory response in vascular adventitial not only involved in hypertension, but also in atherosclerosis and vascular restenosis. As the important composition of outer membrane, perivascular adipose tissue (PVAT) secretes a variety of biological active substances involved in regulation of vascular pathophysiology function. Our previous study found that PVAT secretes inflammatory factors involved in vascular remodeling in DOCA-salt hypertensive model. And the expression of inflammatory factor is regulated by many factors at the transcription and post-transcription level. MiRNAs